REMARKS

The invention features chimeric isoprenoid synthase polypeptides. These chimeric polypeptides are generally useful for a variety of agricultural, pharmaceutical, industrial and commercial purposes by improving isoprenoid synthesis.

Examination of claims 1- 9 is reported in the present Office Action. Claim 6 is objected under 37 CFR § 1.75 (d)(1). The Office Action also includes a Notice to Comply with Sequence Requirements under 37 C.F.R. §§ 1.821-1.825. Claims 1-9 are rejected under 35 U.S.C. 112, first and second paragraphs. Claims 1-5 and 7-9 are rejected under 35 U.S.C. § 102(e) and claims 1-4, 6 and 7-9 are further rejected under 35 U.S.C. § 101. Each of these rejections is addressed below.

Objection under 37 C.F.R. §§ 1.821-1.825

The Examiner asserts that the application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 because, in the Examiner's view, the specification discloses nucleic acid sequences and/or protein sequences in Figure 4A and Table 1, and these sequences are not provided in the sequence listing or the Computer Readable Form (CRF). This objection is respectfully traversed.

In accordance with 37 C.F.R. § 1.821(b), "[p]atent applications which contain disclosures of nucleotide and/or amino acid sequences...shall...conform...to the requirements of §§ 1.821 through 1.825." Figure 4A shows a series of schematic representations of chimeric isoprenoid synthase polypeptides. Table 1 shows that amino acid substitutions at various amino acid positions in the HVS or TEAS isoprenoid

synthase polypeptides can affect the identity of the dominant product of the chimeric isoprenoid synthase enzyme. Figure 4A and Table 1 each fails to disclose any nucleic acid and/or protein sequences, and the application does comply with the requirements of 37 C.F.R. §§ 1.821-1.825, since appropriate sequence listings have been provided where necessary.

Objection to claim 6 under 37 CFR § 1.75(d)(1)

Claim 6 is objected to under 37 CFR § 1.75(d)(1) as being stated as an improper Markush group. This claim has now been cancelled, thus rendering this objection moot.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-9 are rejected under 35 U.S.C. § 112, first paragraph as being supported by an inadequate written description. The Examiner states that "[c]laims 1-9 are directed to all possible combinations of chimeric isoprenoid synthase catalyzing any cyclization reaction involving geranyl diphosphate, farsenyl diphosphate, geranylgeranyl diphosphate or any other natural or man made related structure," while the specification "only provides a single representative species encompassed by these claims involving plant tobacco TEAS or *Hyoscymaus* [sic] HVS genes." The Examiner asserts that the specification fails to sufficiently describe representative species of these chimeric isoprenoid synthases by structural characteristics or properties other than their ability of producing isoprenoid products.

Applicants respectfully submit that a representative number of species is in fact provided by the present specification. As an initial matter, Applicants note that the specification, at pages 9 to 11, discloses 14 different chimeric isoprenoid synthase species (CH1 to CH14) produced by joining together TEAS and HVS, or domains thereof. Even accepting for the sake of argument the Examiner's position that chimeric isoprenoid synthases produced from TEAS and HVS comprise a single species, the written description guidelines state that:

> There may be situations where one species adequately supports a genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a representative number" depends on whether one skilled in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.[1]

Such a situation is presented here. At the time the present application was filed, numerous isoprenoid synthases were known in the art—references describing such enzymes are provided on page 5 of the specification—and the level of knowledge was high. As the level of knowledge in the art was high, the number of species necessary to satisfy the requirement of a "representative number" is low.

Further, Applicants submit that even a single species would have fulfilled the "representative number" requirement. Footnote 54 of the Written Description examination guidelines cites *In re Rasmussen* 650 F.2d 212, 211 USPQ 323

---

[1] . *Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112 First Paragraph, "Written Description" Requirement* Federal Register Vol. 66, No.4, p 1099-1111.

(CCPA 1981) as an example of a situation in which a single species was deemed to be a representative number:

> Disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered.

Thus, if only one species had been disclosed, as is asserted by the Examiner, the facts in the present case would nonetheless be similar to those in *Rasmussen*, in which case the disclosure of the single species would have been sufficient to satisfy the written description requirement.

Applicants disclose the fusion of any two isoprenoid synthases to produce a chimeric isoprenoid synthase, and demonstrate the operability of a series of representive chimeric isoprenoid synthases. One skilled in the art reading the present specification would recognize that any isoprenoid synthase polypeptides might be employed according to the invention. In short, the choice of the parent enzyme used is unimportant to the success of this invention. Furthermore, since one skilled in the art would immediately understand how to construct such a chimeric isoprenoid synthase based on the teachings of the specification, no structural motifs are required for the present invention. In view of the foregoing arguments, applicants respectfully request that this rejection be withdrawn.

Enablement

Claims 1-9 are further rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner states that while molecular biology techniques for making the chimeric isoprenoid synthases are well developed and the level of skill is high, "how to engineer a desired substrate specificity in isoprenoid synthases, and engineering a specificity for product formation is lacking." The Examiner further asserts that "one skilled in the art would require additional guidance, such as information regarding the structure bases for the substrate and product specificities, the identification of various structural elements in various isoprenoid synthases, [and] the conservation of various structural elements of isoprenoid synthases among plants, bacteria, fungus and mammals." Applicants respectfully traverse this rejection.

Applicants first note that, to practice the invention, one skilled in the art does not need to identify desired substrate specificities. Rather, all that is required is a chimeric isoprenoid synthase be made by joining two isoprenoid synthases. As is acknowledged by the Examiner, one of ordinary skill in molecular biology could readily join two polypeptides (or two polynucleotides, each encoding a polypeptide) to produce a chimeric polypeptide. One of ordinary skill in the art could further identify a polypeptide as being an isoprenoid synthase (i.e., a polypeptide that is capable of catalyzing a reaction involving the intramolecular carbon-carbon bond formation of an allylic diphosphate substrate to an isoprenoid product) using any of a number of standard assays. In order to practice the invention, one need not have any knowledge regarding the substrate and product specificities, the identification of various structural elements in various

isoprenoid synthases, or the conservation of various structural elements of isoprenoid synthases among plants, bacteria, fungus and mammals. In view of the foregoing, applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-9 are rejected for indefiniteness on several grounds. First, the Examiner asserts that "the phrase 'comprising a first isoprenoid synthase polypeptide joined to a second, different isoprenoid synthase polypeptide' does not clearly set forth the metes and bounds of the patent protection desired." Applicants respectfully traverse this rejection.

Applicants note that an isoprenoid synthase is clearly defined in the specification as "a polypeptide that is capable of catalyzing a reaction involving the intramolecular carbon-carbon bond formation of an allylic diphosphate substrate to an isoprenoid product." From this definition, one skilled in the art would readily understand that a chimeric isoprenoid synthase need not be the product of two full-length proteins joined together, but can simply be a fragment of an isoprenoid synthase, the fragment having catalytic activity. One would also understand that a chimeric isoprenoid synthase need not be "a fragment of a first [isoprenoid synthase] . . . fused to a complementary fragment of another isoprenoid synthase," as suggested by the Examiner. Quite simply, a chimeric isoprenoid synthase is the product of two isoprenoid synthases, defined above, that have been joined together.

Regarding the remaining rejections, claim 4 is rejected on the basis that the phrase "catalyzes at least two different isoprenoid reaction products" rendered the claim indefinite. Applicants have amended claim 4 to recite that the chimeric isoprenoid synthase "catalyzes the production of at least two different isoprenoid products," as suggested by the Examiner. In view of the present amendment, the rejection of claim 4 for indefiniteness may be withdrawn. Claims 6-9 are also rejected for indefiniteness. Applicants have cancelled these claims, thus rendering this rejection moot.

Rejections under 35 U.S.C. § 102(e)

Claims 1-5 and 7-9 are rejected as being anticipated by U.S. Patent No. 5,744,341 to Cunningham et al. (hereafter "the '341 patent"). According to the Examiner, "[t]he '341 patent teaches two isoprenoid synthase[s] named β-cyclase and ε-cyclase from Arabidopsis thaliana . . . They teach the formation of chimeric cyclase[s] by replacing homologous regions in one gene by another and thereby produce an enzyme with novel function, characteristics and products." Applicants respectfully traverse this rejection.

The central premise on which the Examiner's rejection is based—that these cyclases are isoprenoid synthases—is flawed. The cyclases described in the '341 patent and referred to by the Examiner are lycopene cyclases. Lycopene cyclases are not isoprenoid synthases because they are not "capable of catalyzing a reaction involving the intramolecular carbon-carbon bond formation of an allylic diphosphate substrate (for example, a C_{10}, C_{15}, or C_{20} allylic diphosphate substrate) to an isoprenoid product (for example, a monoterpene, diterpene, sesquiterpene, or sterol product)" (page 5, lines 11-

15). In contrast to the isoprenoid synthase of the invention, a lycopene cyclase catalyzes the conversion of carotene to lycopene. This conversion does not involve the intramolecular carbon-carbon bond formation of an allylic diphosphate substrate, as is required for an enzyme to be considered an isoprenoid synthase. Consequently, the lycopene cyclases described in the '341 patent are not isoprenoid synthases.

As the '341 patent fails to describe a chimeric isoprenoid synthase polypeptide that includes a first isoprenoid synthase polypeptide joined to a second, different isoprenoid synthase polypeptide, as is required in each of the pending claims, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-5 and 7-9 as being anticipated by the '341 patent.

Double patenting rejections

Claim 6 was rejected for statutory type double patenting in view of claim 5 of U.S. Patent No. 5,824,774 (hereafter "the '774 patent"). Since Applicants have cancelled claim 6, this rejection is now moot.

Claims 1-4 and 7-9 were rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1-8 and 15-18 of the '774 patent. Applicants have overcome this rejection by filing a terminal disclaimer, enclosed herewith. Accordingly, this rejection may now be withdrawn.

Conclusion

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the Office action for two months, to and including January 6, 2003 and a check in payment of the required extension fee $205.00. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: January 6, 2003

Susan M Michaud

Paul T. Clark
Reg. No. 30,162

Susan M Michaud
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

Marked-up version of amended claims

4. (Amended) The chimeric isoprenoid synthase polypeptide of claim 1, wherein said chimeric isoprenoid synthase polypeptide catalyzes the production of at least two different isoprenoid reaction products [at least two different isoprenoid reaction products].